--13. A method of antagonizing or partially agonizing the effect of human interleukin-4 (hIL-4) comprising contacting cells expressing the hIL-4-receptor with an antagonistic or partially agonistic effective amount of a mutant hIL-4 protein according to claim 3.--

--14. A method of antagonizing or partially agonizing the effect of human interleukin-4 (hIL-4) comprising contacting cells expressing the hIL-4-receptor with an antagonistic or partially agonistic effective amount of a mutant hIL-4 protein according to claim 4.--

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefor. Please charge the required petition fee to Deposit Account No. 02-1445.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess to our Deposit Account No. 02-1445.

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

At the outset, Applicants wish to thank Examiner Draper for the courtesy of the interview recently accorded Applicants' representative, and, in particular, for her careful preparation and for her helpful suggestions. Where possible, Applicants have endeavored to adopt these suggestions.

The application was objected to because of certain informalities. In response, Applicants have revised the Sequence Listing under separate cover. Please see the separate response dated September 1, 1998.

Applicants have changed the periods used in the recitations of the U.S. patents on page 3 of the specification to commas. Applicants checked the remainder of the specification and this appears to be the only instance of such misuse of periods.

Also, Applicants have amended the specification to provide the suggested headings and subheadings.

However, under point 2b on page 2 of the Office Action, the Examiner objected to the abbreviation "cf." This issue was not discussed at the interview in any depth, but Applicants are not certain exactly what needs to be corrected, and respectfully request the Examiner's help in clarifying this point.

Claims 1 and 2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S.

Patent No. 5,723,118. In response, Applicants note that here and elsewhere in the Office Action the Examiner has stated that the instant proteins have modifications "at residues 121, 124 and/or 125 either alone, or in combination with other modifications on the IL-4." However, as can be seen from claim 3, the instant proteins are "characterized in that, in addition to replacements at positions 121, 124 or 125, modifications are also present . . ." Consequently, the instant proteins never are characterized solely by modifications at positions 121, 124 and/or 125. Instead, the instant proteins always have a second modification somewhere else in the molecule. This second modification is at the N-terminus, the C-terminus, in potential glycosylation sites and/or in the coupling of the protein to a non-protein polymer.

The foregoing is important, of course, because the Examiner characterizes the claims of the cited reference as overlapping in scope with the instant claims. However, the claims of the cited reference embrace only muteins having a single modification as compared to hIL-4, namely the residues at positions 121, 124 and/or 125 are replaced by another amino acid or the protein is terminated at position 121, 124 or 125. Thus, the claims of the cited reference do not, in fact, embrace muteins having a second modification of the type discussed above, which is required by the muteins of the instant claims. Consequently, the claims do not, in fact, overlap, and there is no obviousness-type double patenting.

In order to emphasize this "second" modification, the original claims have been completely revised to make clear that the instant proteins comprise two types

of modifications as compared to wild-type hIL-4. The first modification involves replacement of one or more of the residues at positions 121, 124 and/or 125. The second modification involves one or more changes at the N-terminus, the C-terminus, in potential glycosylation sites and/or in the coupling of the protein to a non-protein polymer. New main claim 3 embodies these revisions and clearly is supported by original claim 1. Clauses a) and b) of new claim 4 are supported by, for example, page 2, lines 14-16; and clause d) is supported by page 3, lines 11-13. New claim 5 is supported by page 4, lines 26-30. Clause a) of new claim 6 is supported by page 5, lines 7-10; and clause b) is supported by page 3, line 11. No new matter has been added.

Applicants have added method of use claims 11-14. To the extent that the Examiner considers these claims to be separate and distinct from the subject matter of original claims 1 and 2, then Applicants have constructively elected new claims 3-10 by original presentation. However, if claims 11-14 are withdrawn from consideration, then Applicants presume that these claims will be rejoined and examined in the event that any of claims 3-6 are found to be allowable in accordance with the Commissioner's Notice published in the Official Gazette on March 26, 1996, at 1184 OG 86. According to that notice:

> "[A]pplicant may be called upon under 35 U.S.C. § 121 to elect claims to either the product or the process. The claims to the non-elected invention will be withdrawn from further consideration. However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from and otherwise includes all the limitations of an allowed product claim."

Consequently, in the event that claims 11-14 are withdrawn from consideration, Applicants would appreciate an indication that the Examiner is proceeding in accordance with this notice, and that claims 11-14 will be rejoined and examined in the event that any one of claims 3-6 is found to be allowable. If the Examiner is not proceeding in accordance with this notice, then Applicants would appreciate an explanation from the Examiner of why this notice is not applicable.

Claims 1 and 2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-22 and 25 of co-pending U.S. Application Serial No. 08/897,202.

Claims 1 and 2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of co-pending U.S. Application Serial No. 08/874,697.

In response to both of the immediately preceding obviousness-type double patenting rejections, Applicants respectfully request that these be held in abeyance until allowable subject matter is indicated in one of the cases involved. At that time, Applicants will reassess the situation and proceed accordingly.

For the record, Applicants would point out that any patent issued on the present case definitely will expire before any patent issued on either of the two cited applications. Accordingly, the propriety of rejecting the instant application on the ground of obviousness-type double patenting is immediately in question since the

patent issuing from the instant application could never time wise extend the "right to exclude" granted by either patent issued on the cited applications.

Claims 1 and 2 were rejected under 35 USC § 103(a) as being obvious over U.S. Patent No. 5,723,118 (Sebald). In response, Applicants refer to and incorporate the discussion above concerning the relationship of the instant claims to the disclosure of Sebald. The disclosure of Sebald describes only muteins having a single modification as compared to hIL-4, namely the residues at positions 121, 124 and/or 125 are replaced by another amino acid or the protein is terminated at position 121, 124 or 125. Thus, the disclosure of Sebald does not, in fact, embrace muteins having a second modification of the type discussed above, which is required by the muteins of the instant claims. Consequently, there is no overlap and no obviousness.

Claim 2 was objected to as being a substantial duplicate of claim 1. In response, as noted above, Applicants have revised the original claims. Claim 2 is replaced by new claims 7-10, which are in the conventional "composition" claim format. These claims clearly are not duplicates of claims 3-6 by virtue of the requirement in claims 7-10 of an additional "physiologically acceptable carrier."

Claims 1 and 2 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. In response, Applicants point out that the enablement question must be resolved against the backdrop of the Sebald patent, U.S. Patent No. 5,723,118. Dr. Sebald is one of the co-inventors on the instant application, and during the prosecution of his prior patent he was allowed coverage

to hIL-4 muteins, which "[had] the amino acid sequence of wild-type hIL-4 protein, but wherein one or more of the amino acids occurring therein at positions 121, 124 or 125 is replaced by another natural amino acid." Consequently, the Patent Office is already on record as determining the enablement for the full scope of changes presently claimed at these positions, and the Examiner should give full faith and credit to that determination.

Accordingly, the enablement question here really boils down to whether there is reasonable assurance that the "second modifications" required here could be made without affecting operability. Applicants submit that the Examiner has not made out a case that reasonable assurances are lacking here. In fact, in connection with the second obviousness rejection, the Examiner has taken the position that two of the four "second modifications" were state of the art. Since a prima facie case of obviousness requires that the cited references reveal a reasonable expectation of success, it follows that if the Examiner has, in fact, made out a prima facie case of obviousness, then the Examiner has also satisfied herself as to the reasonable assurance allegedly missing here.

The real issue appears to be predictability, i.e., the Examiner cannot tell beforehand which muteins will have the desired property and which will not. However, Applicants submit that enablement does not require this. It is enough that Applicants have explained how to make muteins and then test them for the desired property. Moreover, the methods used to make the muteins and to test them were state of the art at the time the invention was made, and further the

Examiner has not contested this.

Applicants admit that some experimentation would be required in order to practice the full scope of the invention. However, Applicants submit that any such experimentation is not undue.

As the Court in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), explained, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." Further, on the same page, they quoted with approval the following quote from In re Jackson, 217 USPQ at 807 (POBA 1982):

> "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction the experimentation should take. [Emphasis added.]"

Not only is any experimentation required here straight-forward, conventional and routine, but the specification also provides a reasonable amount of guidance with respect to the direction the experimentation should take. Accordingly, both prongs of the Jackson "test" are met and, therefore, although some experimentation would be required to practice the full scope of the instant invention, as the Examiner urges, any required experimentation is not undue.

On the issue of predictability, Applicants would call the attention of the

Examiner to the decision in Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989), wherein the Board of Appeals found a specification was enabling despite the fact that there was actual evidence of inoperability, thereby, leading to a total lack of predictability. (As will be explained below, the present case is, thus, "better" since there is no actual evidence of inoperability.)

The invention in Mark required the identification in a native protein of free cysteine groups that were nonessential to the biological activity of the native protein. The claims related, among other things, to muteins in which at least one of the identified nonessential cysteines was replaced by another amino acid. The essence of the invention was the discovery that the muteins retained the biological activity of the native protein.

However, as stated above, the invention was completely unpredictable. In other words, it was not clear beforehand which cysteines were "nonessential" and, therefore, could be replaced without a loss of the biological activity of the native protein.

Indeed, as stated above, there was actual evidence that certain cysteines could not be replaced without a loss of the biological activity of the native protein. Thus, there was prior art that showed that a mutein having a specific cysteine → tyrosine replacement did not retain the biological activity of the native protein. In addition, there was data in a related application of applicants therein, which showed that seven other cysteine → serine substitutions resulted in a substantial reduction in

biological activity.

Against this backdrop, the examiner therein found that it would require undue experimentation to construct the "innumerable" muteins encompassed by the claims therein and then to screen the muteins produced to determine which retained biological activity. (These arguments are nearly identical to those made by the Examiner here.)

The examiner therein pointed to the loss of activity with the substitutions mentioned above. The examiner therein also pointed out that most cysteines were essential to proper protein folding and, thus, activity and, consequently, most of the muteins prepared by applicants therein would be expected to be less active than the native protein. Further, the examiner therein also took the position that the mere sequencing of all possible proteins encompassed by the claims would entail undue experimentation.

In spite of what the examiner therein undoubtedly viewed as a very good case for nonenablement, the Board decided in favor of applicants therein.

The reasons for that decision merit very close examination.

The Board noted that a declaration was provided that set forth a "reasonable", "step-by-step" scheme, which, if followed, would allow a person of ordinary skill in the art to determine in a simple, straight-forward manner whether

a given cysteine was essential or nonessential. In other words, it was routine to determine whether a particular embodiment was operative. (Although no similar declaration is submitted here, such does not require a finding of no enablement. A declaration cannot fix a fatally defective specification. Thus, Applicants here submit that what ultimately is important is that the Board therein pointed out that the step-by-step scheme in the declaration "parallels the disclosure". See Mark, 12 USPQ2d at 1906.)

Also, the claims therein were limited by functional language to only operative embodiments.

Given the foregoing, the Board found that the disclosure was enabling because the claims were expressly limited to muteins that retained biological activity and the specification set forth a step-by-step scheme by which it could be determined whether a given mutein retained biological activity. Although operability was highly unpredictable, the Board reasoned that one skilled in the art would be able to routinely determine whether a given cysteine was nonessential and, therefore, when replaced or deleted would result in a mutein within the claims therein.

In the present case, the Examiner concedes that the specification sets forth a step-by-step scheme by which one of ordinary skill in the art is able to prepare hIL-4 muteins and test for the desired property. Accordingly, the specification should be found enabling for the claimed hIL-4 muteins.

Moreover, even assuming, for the sake of argument, that the Examiner's concerns about predictability are well-founded and certain embodiments might be inoperative, such embodiments are not within the present claims since the present claims expressly require that the mutein "[be] an antagonist or partial agonist of wild-type hIL-4." Thus, the instant claims provide the same "functional" language "safeguards" as were provided by the claims in Mark.

In view of the foregoing, Applicants submit that the present claims satisfy the enablement requirement. An early notice to that effect is earnestly solicited.

Claims 1 and 2 were rejected under 35 USC § 102(a) as being anticipated by or, in the alternative, under 35 USC § 103(a) as being obvious over Tony et al. ("Tony"), Eur. J. Biochem., 225: 659 (1994), Kruse et al. ("Kruse I"), FEBS Lett., 286: 58 (1991), Kruse et al. ("Kruse II"), EMBO J., 11: 3237 (1992), or Kruse et al. ("Kruse III"), EMBO J., 11: 789 (1992). In response, Applicants point out that all of these references teach only muteins having a single modification as compared to hIL-4, namely the residues at positions 121, 124 and/or 125 are replaced by another amino acid or the protein is terminated at position 121, 124 or 125. Consequently, these references do not, in fact, teach or suggest muteins having a second modification of the type discussed above, which is required by the muteins of the instant claims. Accordingly, the instant claims are neither anticipated nor rendered obvious by these references.

In this regard, Tony teaches the double muteins a) R121D/Y124D, b)

R121D/S125D and c) Y124D/S125D; and the triple mutein R121D/Y124D/S125D. These muteins are unaltered in other portions of the molecule, and therefore lack the "second modification" required by the instant claims. Consequently, the reference proteins do not anticipate or render obvious the instant claims.

Kruse I discloses only the single mutein Y124D. This mutein is also unaltered in other portions of the molecule, and therefore lacks the "second modification" required by the instant claims. Consequently, the reference protein does not anticipate or render obvious the instant claims.

Kruse II discloses the single muteins Y124F, Y124H, Y124N, Y124K, Y124G and Y124D. These muteins are also unaltered in other portions of the molecule, and therefore lack the "second modification" required by the instant claims. Consequently, the reference proteins do not anticipate or render obvious the instant claims.

Kruse III hints at muteins having replacements at position 124 and one of positions 121 or 125, but does not specify any particular proteins. In any event, these muteins would also be unaltered in other portions of the molecule, and therefore would also lack the "second modification" required by the instant claims. Consequently, the reference proteins would not anticipate or render obvious the instant claims.

Claims 1 and 2 were rejected under 35 USC § 103(a) as being obvious over any

one of Tony, Kruse I, Kruse II or Kruse III taken in view of Anderson et al. ("Anderson") or Francis. In response, Applicants point out that the thrust of this rejection was that the primary references anticipated or rendered obvious the instant muteins and it would have been obvious to modify the proteins of the primary references further as taught by Anderson or Francis to achieve other of the claimed muteins. However, it has been explained above how the primary references do not anticipate or render obvious the present claims. Consequently, modification of the proteins of the primary references further as taught by Anderson or Francis should not yield the claimed muteins.

Applicants believe the foregoing constitutes a full and complete response to all outstanding objections and rejections.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on the date indicated below:

Date October 1, 1998

By _____
Kurt G. Briscoe